Remarks

It is requested that the foregoing amendment be entered and that the rejections be reconsidered. Claims 1-63 are pending in the application and claims 1-63 are rejected. In this response, claims 2, 6, 11, 13, 18, 19, 25, 32, 34, 35, 43, 45, 46 and 48 have been amended, claims 55-63 have been cancelled, and new claims 64-72 have been added. Applicants submit that these amendments and additions to not present any new matter. Applicants additionally respectfully submit that in view of the arguments presented below, the claims are now in condition for allowance.

I. Addition, Amendment and Cancellation of Claims:

Applicants have amended claims 2, 6, 11, 13, 18, 19, 25, 32, 34, 35, 43, 45, 46 and 48 to more particularly claim the present invention, and Applicants assert that support for these amendments can be found throughout the specification. Additionally, claims 64-72 have been newly added, support for which can also be found throughout the specification. Finally, claims 55-63 have been canceled in an effort to expedite prosecution, however Applicants are not canceling these claims to concede the correctness of the Examiner's stated rejection. Rather Applicants explicitly reserve the right to pursue the subject matter of these claims in a continuing application.

II. Rejection under 35 U.S.C. § 112, first paragraph:

A) The Examiner has rejected claim 55 under 35 U.S.C.§ 112, first paragraph, and asserts that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In an effort to expedite prosecution, Applicants have cancelled claim 55 and thus respectfully assert that the rejection is now moot. Applicants are not, however, canceling this claim to overcome the Examiner's rejection, and Applicants explicitly reserve the right to pursue canceled claims 55-63 in a continuing application.

B) The Examiner has also rejected claims 12, 16, 22, 23, 31, 41, 42 and 55-63 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As stated above, this rejection is now moot with respect to claims 55-63, however Applicants address the Examiner's rejection of claims 12, 16, 22, 23, 31, 41 and 42 below.

The Examiner first asserts that the specification fails to disclose any specific hapten/antibody complex, or methods of fabricating such within a polymer, such as the disclosed nanosphere. The Examiner states that although antibody binding to the surface of nanospheres and other polymers are routine in the art for targeted delivery, it is not generally known in the art the use of a hapten for use in conjunction with the antibody, or how such would even be fabricated. The Examiner thus asserts that it would require undue experimentation by one of ordinary skill in the art to make and use a composition comprising a hapten/antibody anchor-tag complex in a biodegradable polymer.

Applicants respectfully disagree and assert that the Examiner has not construed the claims properly, which is the first requirement in the assessment of any enablement rejection under 35 U.S.C. § 112, first paragraph, and thus the Examiner has not established a *prima facie* case of lack of enablement. Before discussing the enablement rejection in more detail, Applicants would first like to point out that Applicants invention provides for the incorporation of an anchor moiety within a biodegradable polymer, so that the anchor moiety is available on the surface of the biomaterial architecture for the facile attachment of biologically relevant molecules using biomolecular recognition events. The ability to effectively attach ligands to the polymer surface via biomolecular interactions is particularly useful for the post-fabrication modification of architecture surfaces, because it is often difficult to effect post-fabrication attachment of ligands to certain biomaterial architectures via covalent interactions because of either the harsh conditions required for covalent attachment which can compromise the biomaterial architecture, or the masking of available functional groups by surfactants. Significantly, Applicants novel polymer composition and methods allow for the facile and efficient attachment of ligands to biomaterial architectures using mild conditions that will not compromise the biomaterial architectures and is widely applicable for attachment of many

different classes of ligands.

Specifically addressing the enablement rejection, Applicants respectfully point out (as exemplified in Example 3 in the specification) that a hapten/antibody *complex* would not be fabricated *within* the polymer as the Examiner suggests; rather, the polymer, as disclosed in the Examples, is fabricated with an anchor moiety (e.g., antibody) incorporated therein. As disclosed on page 8, lines 4-10, an antibody fragment may be covalently bound to a block copolymer in the synthesis of the biodegradable polymer. For example, the antibody or fragment thereof may be covalently bound to a block copolymer containing a polyalkylene glycol by reaction with the terminal hydroxyl group of the polyalkylene glycol. After the biodegradable polymer having an anchor incorporated therein has been synthesized, the polymer is then either fabricated into a desired biomaterial architecture (such as a scaffold, nanoparticle, microparticle) or can also be directly contacted with an adapter moiety or contacted directly with the tag-ligand moiety. Clearly, any contact between the adapter moiety (e.g., hapten) and the surface of the biomaterial architecture where the available antibodies are exposed, occurs in the *postfabrication* stage. Specifically, once the antibody is incorporated into the polymer (and then the polymer is fabricated further, or even utilized directly) the architecture is then, according to the method of the invention, contacted with a hapten to effect an antibody-hapten interaction, and then finally the complex is contacted with a ligand-tag moiety (e.g., a desired ligand having an antibody complex attached thereto). Applicants respectfully assert that utilization of a hapten/antibody interaction would not require undue experimentation because the specification provides guidance for the synthesis of a biodegradable polymer having an antibody anchor incorporated therein, and a person of ordinary skill in the art would be able to select and/or generate appropriate antibody/hapten pairs to ultimately provide a hapten that can then be complexed with the antibody that has been incorporated into the polymer synthesis (which antibody would be exposed on the surface of the polymer and available for interaction). Applicants thus respectfully assert that the claims are indeed enabled for the use of biomolecular interactions to effect attachment of ligands to biomaterial architectures, including the use of antibody/hapten interactions to effect the attachment of ligands to the surfaces of biomaterial architectures. In view of the arguments presented above, Applicants respectfully request that the Examiner withdraw the rejection of claims 12, 16, 22, 23, 31, 41 and 42.

III. Rejection under 35 U.S.C. § 112, second paragraph:

The Examiner has rejected claims 55-63 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that claims 55-63 are unclear as to the use of "ligand" and "therapeutic agent" with the composition, and would like clarification regarding their association with the composition. In an effort to expedite prosecution, Applicants have cancelled claim 55 and thus respectfully assert that the rejection is now moot. Applicants are not, however, canceling this claim to overcome the Examiner's rejection, and Applicants explicitly reserve the right to pursue canceled claims 55-63 in a continuing application.

III. Rejection under 35 U.S.C. § 102(a):

The Examiner has rejected claims 1-11, 13-15, 17-21, 24-30, 32-40 and 43-54 under 35 U.S.C. § 102(a) as being anticipated by Patel *et al.* (11/98).

Applicants respectfully submit that Patel *et al* (11/98) is not an anticipatory reference because the invention was not known or used by others in this country, or patented or described in a printed publication in this or a foreign country before the invention thereof by the applicant for a patent. Specifically, the reference cited by the Examiner includes several different authors, however, only certain of these authors are inventors of the presently claimed subject material. It is believed that the authors on the paper that are inventors of the claimed invention include Scott M. Cannizzaro, Robert Langer, and Kevin M. Shakesheff. A *Katz* declaration executed by Scott M. Cannizzaro using the procedure under 37 C.F.R. § 1.132 is submitted herewith to that effect. Executed declarations from the other inventors Robert Langer and Kevin M. Shakesheff have not yet been provided, however, as soon as signed declarations can be obtained from these inventors, they will be submitted immediately for consideration by the Examiner in the Patent and Trademark Office.

Applicants respectfully request that the Examiner consider the 1.132 declaration and withdraw the rejection under 35 U.S.C. § 102(a).

III. Rejection under 35 U.S.C. § 103(a):

The Examiner has rejected claims 1-11, 13-15, 17-21, 24-30, 32-40, and 43-54 under 35 U.S.C. § 103(s) as being unpatentable over Bhat *et al.* (4/1998) in view of Domb *et al.* Specifically, the Examiner asserts that Bhat *et al.* teach the use of avidin-biotin complexes attached to glass substrates and to which aortic endothelial cells were attached, resulting in increased initial cellular spreading rates and strength of attachment. The Examiner further points out that Bhat *et al.* do not teach the use of biodegradable polymers with the avidin-biotin complex. The Examiner also states that Domb *et al.* teach the use of biodegradable polymers, such as a PLA-PLG nanosphere, to which molecules are covalently bound to the surface for targeted delivery. The Examiner thus asserts that in light of Bhat and Domb *et al.*, it would have been obvious to one of ordinary skill in the art to make a composition comprising a biodegradable polymer, such as PLA-PEG complex, and to which a biotin-avidin complex were attached. The Examiner further asserts that one would have been motivated to do this in order to use the composition to facilitate the attachment of the polymer to cells in the hopes of improving the efficacy of tissue differentiation as displayed by Bhat *et al.* The Examiner finally states that it would also have been obvious to substitute the glass in the Bhat *et al.* invention with a biodegradable polymer, because such were routinely used *in vivo* and in the art of tissue engineering as scaffolds to support cell migration and differentiation.

Applicants respectfully disagree with the Examiner and assert that a *prima facie* case of obviousness has not been established for several reasons. First, there is no motivation or suggestion in Bhat *et al.* or Domb *et al.* to develop a synthesis for biodegradable polymers having incorporated therein an anchor moiety to facilitate recognition events for the attachment of desired ligands to a biomaterial architecture, or the subsequent use of said novel biomaterial architecture in drug delivery or tissue engineering. Furthermore, Applicants respectfully assert that there is no reasonable expectation of success for the development of a polymer system having an anchor incorporated therein based on the teachings of Bhat *et al.* and Domb *et al.* Finally, even if the references are combined as the Examiner suggests, Applicants respectfully assert that the combination of the teachings of Bhat *et al.* and Domb *et al.* would not yield the claimed invention.

Before discussing each of the points above in more detail, Applicants would first like to point out that Applicants' invention provides for the incorporation of an anchor moiety within a biodegradable polymer, so that the anchor moiety is available on the surface of the biomaterial architecture for the facile attachment of biologically relevant molecules using biomolecular recognition events. The ability to effectively attach ligands to the polymer surface via biomolecular interactions is particularly useful for the post-fabrication modification of architecture surfaces, because it is often difficult to effect post-fabrication attachment of ligands to certain biomaterial architectures via covalent interactions because of either the harsh conditions required for covalent attachment which can compromise the biomaterial architecture, or the masking of available functional groups by surfactants. Significantly, Applicants novel polymer composition and methods allow for the facile and efficient attachment of ligands to biomaterial architectures using mild conditions that will not compromise the biomaterial architectures and is widely applicable for attachment of many different classes of ligands.

Applicants respectfully assert that there is no suggestion or motivation, in either of the cited references, or in the knowledge generally available to one of ordinary skill in the art, to develop a polymer material having an anchor moiety incorporated therein to enable surface modification using biological recognition events. Bhat *et al.* teach the use of an adsorbed film of biotinylated BSA for further coupling to avidin receptor, and make no suggestion to modify polymers to facilitate attachment of ligands to biomaterial architectures. Additionally, Domb *et al.* teach the synthesis and use of block-copolymers, and Applicants assert that Domb *et al.* actually teach away from the incorporation of a separate attachment moiety in the polymer synthesis step, and instead assert that existing functional groups (e.g., the terminal hydroxyl group of poly(alkylene glycol) can be utilized for covalent attachment (see column 13, lines 15-29) after the processing of a microsphere or other architecture has occurred. Clearly, in Domb *et al.* attachment of biological moieties is described or effected through a covalent linkage in the *post-processing* step (that is, after the biomaterial architecture such as a microsphere, has been formulated) and thus, under many conditions, the integrity of the biomaterial architecture may be compromised using conditions to effect the covalent attachment. As described in the specification, Applicants method of producing polymers having an anchor incorporated therein, which are then available on the surface of the architecture to enable surface modification,

represents a significant improvement in the fabrication and modification of the surfaces of biomaterial architectures because mild reaction conditions can be utilized and the inventive techniques can be applied to a wide range of ligands for use in tissue engineering or drug delivery applications. In contrast, Domb *et al.*, and Bhat *et al.* make no suggestion for the use of these improved polymers; rather they rely on traditional methods known in the art to effect attachments, which methods clearly are problematic for many biomaterials applications.

In view of the pioneering nature of Applicants invention, it is further asserted that there would be no reasonable expectation of success to generate the claimed compositions or to use the claimed compositions using the teachings of Domb *et al.* or Bhat *et al.* Domb *et al.* teaches the synthesis of non-linear multi-block co-polymers, however, Domb *et al.* does not provide any teachings or guidance for the incorporation of biologically relevant anchor moieties into the polymer synthesis to effect biological recognition events. As discussed above, Domb *et al.* only provide for the attachment of ligands through a covalent interaction with a reactive surface functionality (e.g., hydroxyl moiety). Additionally, Bhat *et al.* do not even utilize polymers, and only teach the adsorption methods to attach biotin to the glass surface. Clearly, since Domb *et al.* and Bhat *et al* fail to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public (see *In re Hoeksema*, 399 F.2d 269, 274-275, 158 USPQ 597, 601 (CCPA 1968). Thus, Applicants respectfully assert that because Domb *et al.* and Bhat *et al.* fail to disclose or render obvious a method for making the novel polymers or biomaterial architectures having an anchor incorporated therein, it necessarily follows that the compositions and methods for modification of biomaterial architectures according to the present invention are necessarily non-obvious.

Finally, even if, as the Examiner suggests, one were to combine the teachings of Domb *et al.* and Bhat *et al.*, the combination would not yield the claimed invention. Specifically, the replacement of the glass substrate utilized in Bhat *et al.* with the polymer of Domb *et al.* would only result in a biomaterial architecture comprised of a polymer with available functional groups (e.g., hydroxyl groups) for covalent attachment as suggested by Domb *et al.*, and would not result in a polymer architecture having an anchor moiety incorporated therein for utilization in biological recognition events, as claimed in the present application. In order to even attempt

biological recognition events using the polymer of Domb *et al.*, one would have to try to attach the biotin moiety in a post-fabrication step via a functional moiety such as hydroxyl. The benefit of Applicants' composition is that the anchor moiety is incorporated therein and thus is widely available on the surface of the architecture, and thus the surface can be readily modified using mild and effective conditions, thus avoiding any potentially damaging post-fabrication reactions that have proven to be troublesome for the art in general.

In view of the arguments as presented above, Applicants respectfully assert that the claims are now in condition for allowance and thus request that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

Conclusion

Based on the arguments presented above, it is submitted that the pending claims, as amended herein, are allowable over the art of record. Applicants would also like to thank the Examiner for thoughtful comments and careful consideration of the case. If a telephone conversation would help expedite prosecution of this case, please do not hesitate to contact the undersigned at (617) 248-5216. Additionally, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
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